



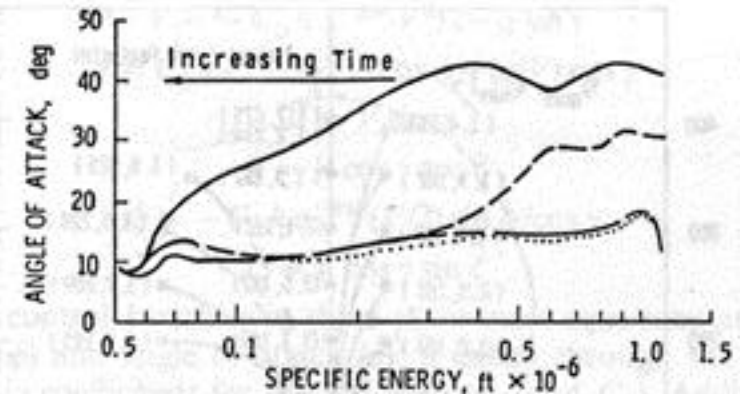
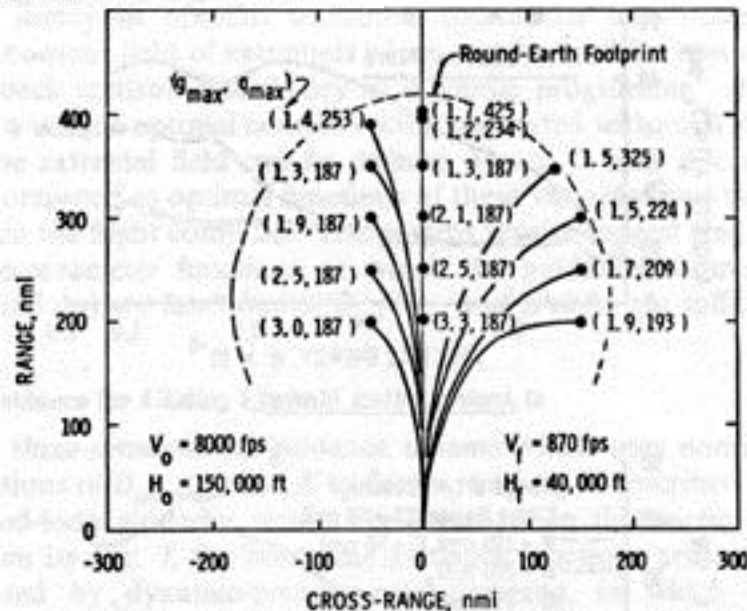
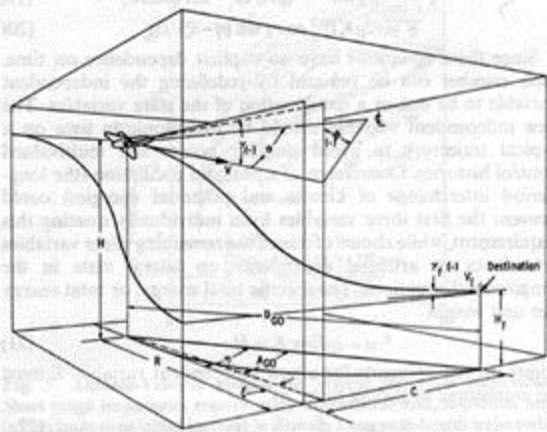
# **Optimal Control: From the Space Shuttle to HIV**

**Robert Stengel  
Princeton University  
October 2002**

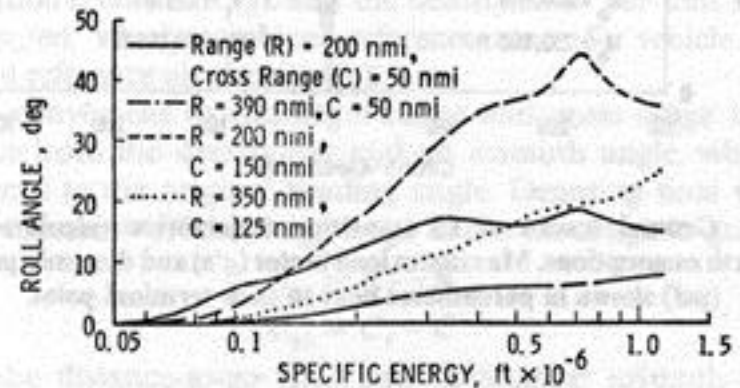


- **Aerospace Optimization**
- **The Immune System**
- **Models of Disease Dynamics**
- **Optimal Therapies and Disease Etiologies**

# Optimal Guidance for Space Shuttle Reentry

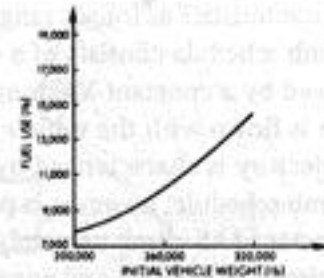
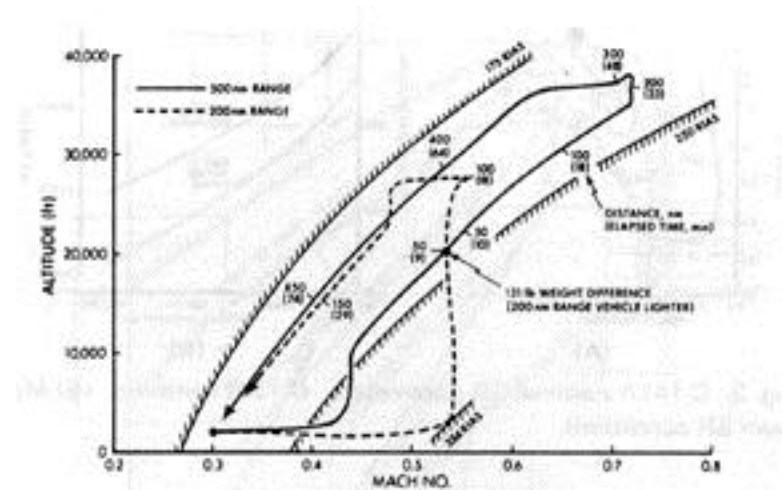


a) Angle-of-Attack History



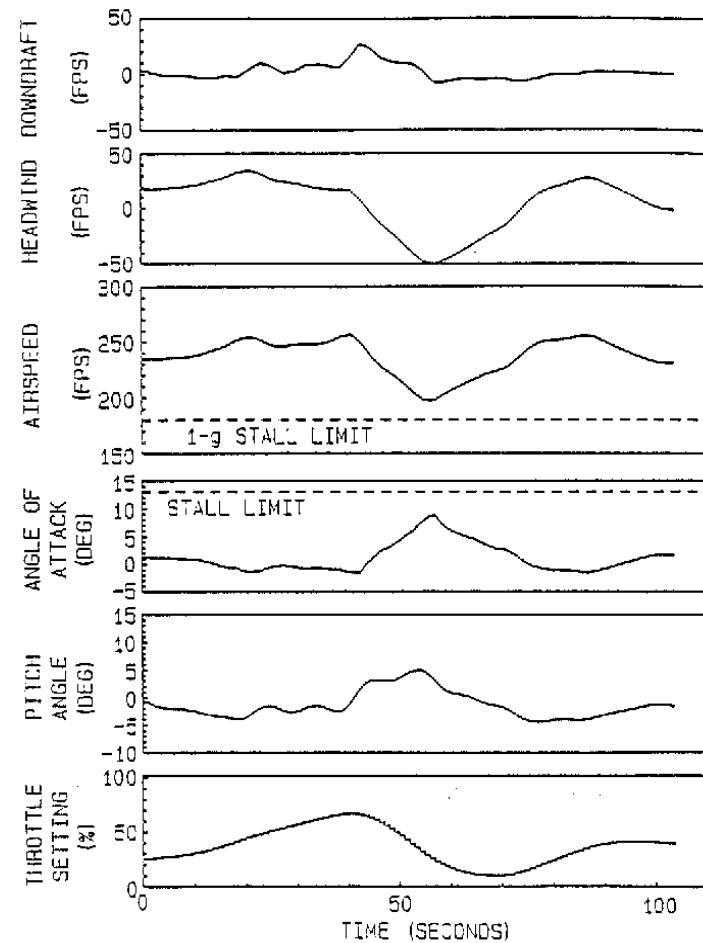
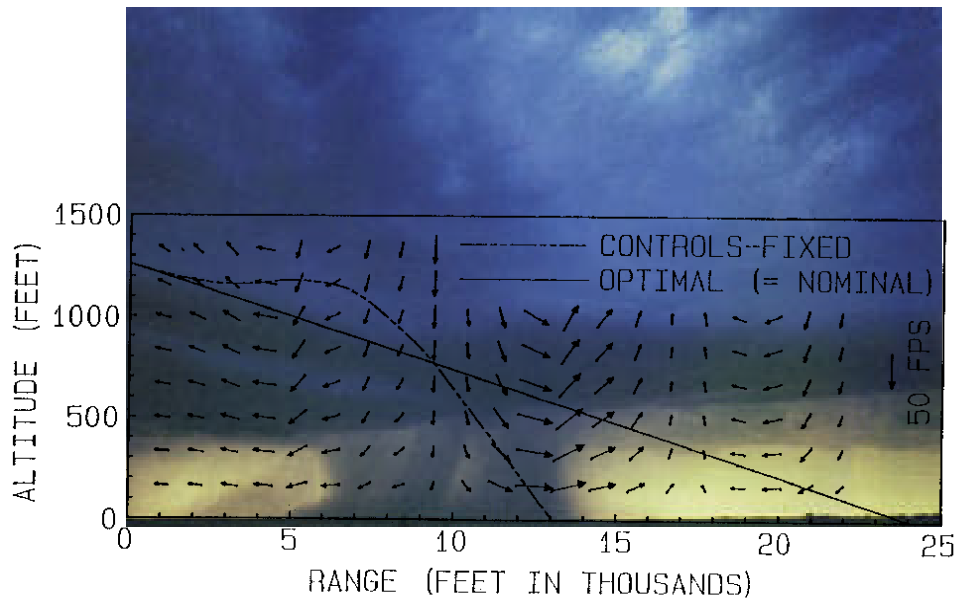
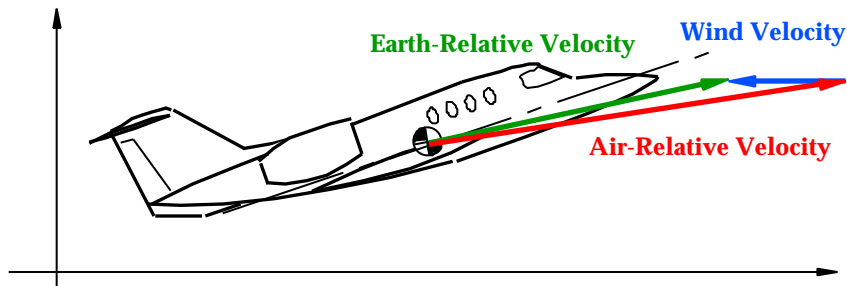
b) Roll Angle History

| Age Group | Percentage |
|-----------|------------|
| 18-24     | ~45%       |
| 25-34     | ~35%       |
| 35-44     | ~25%       |
| 45-54     | ~15%       |
| 55-64     | ~10%       |
| 65-74     | ~8%        |
| 75-84     | ~5%        |
| 85-94     | ~3%        |
| 95-104    | ~2%        |



# Optimal Flight Paths Through Microburst Wind Shear

(w/M. Psiaki, D. A. Stratton, S. Mulgund)



# The Optimal Control Problem



- Minimize a cost function

$$J = \phi[\mathbf{x}(t_f)] + \int_{t_o}^{t_f} L[\mathbf{x}(t), \mathbf{u}(t)] dt$$

- subject to a dynamic constraint

$$\dot{\mathbf{x}}(t) = \mathbf{f}[\mathbf{x}(t), \mathbf{u}(t)]$$

- Define the Hamiltonian

$$H(\mathbf{x}, \mathbf{u}, \lambda, t) = L(\mathbf{x}, \mathbf{u}, t) + \lambda^T \mathbf{f}$$

# The Optimal Control Solution



## ■ Euler-Lagrange equations

$$\dot{\lambda}(t) = - \frac{\partial H[\mathbf{x}(t), \mathbf{u}(t), \lambda(t), t]}{\partial \mathbf{x}}^T$$

$$\lambda(t_f) = \frac{\partial \phi[x(t_f)]}{\partial \mathbf{x}}^T$$

$$0 = \frac{\partial H[\mathbf{x}(t), \mathbf{u}(t), \lambda(t), t]}{\partial \mathbf{u}}$$

## ■ Steepest-descent minimization

$$u_k = u_{k-1} - \varepsilon \frac{\partial H}{\partial u}$$

# Disease Dynamics



## ■ Evolution of disease is a dynamic process

- Pathogenic initial condition
- Growth of pathogen
- Immune response
- Effect of therapy

## ■ Nature of episode depends on dynamic structure, model parameters, and initial conditions

- Sub-clinical response
- Clinical response
- Chronic response
- Lethal response

# Models for Studying Disease Dynamics



## ■ Compartmental models

- Characterization of concentrations of elemental components
- Ordinary differential/difference equations

## ■ Molecular models

- Interactions of molecules and cells
- Partial differential equations, cellular automata

## ■ Gene regulatory networks

- Genes, proteins, ribosomes, cells, organisms
- Compartmental (possibly hybrid) models

## ■ Applications

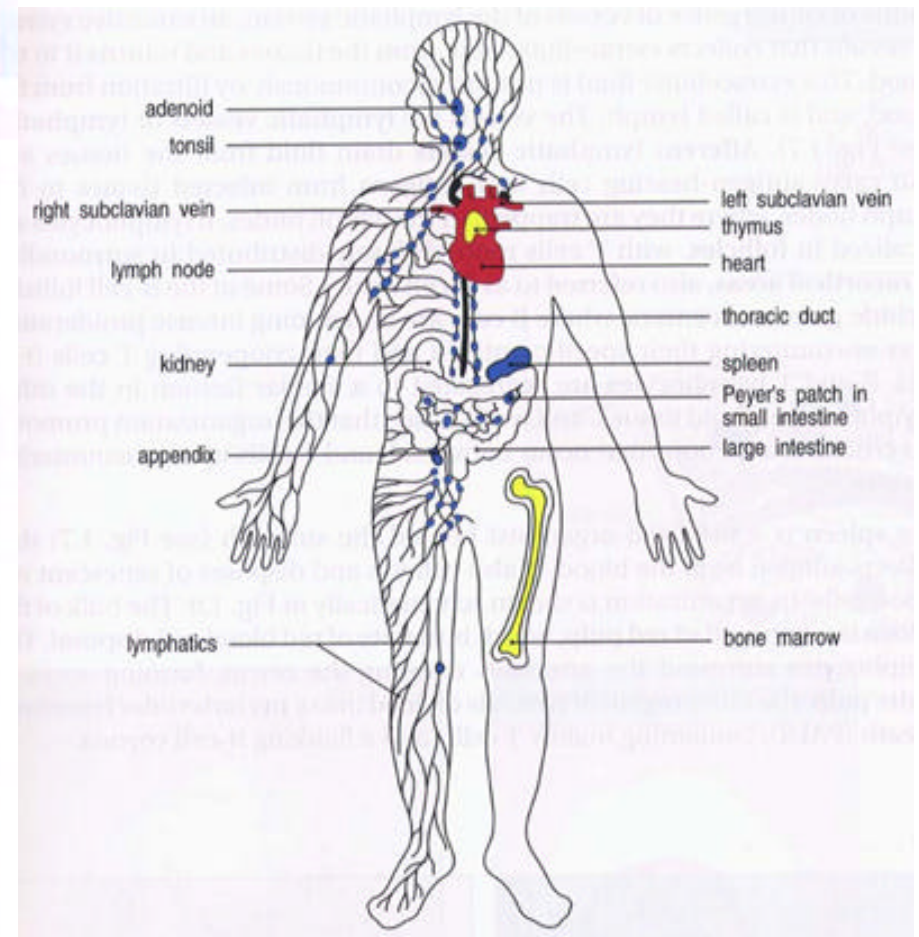
- Immune system, infectious diseases, cancer
- Pharmacokinetics/dynamics

# Infection and the Immune System

(from *Immunobiology*, Janeway et al, 2001)

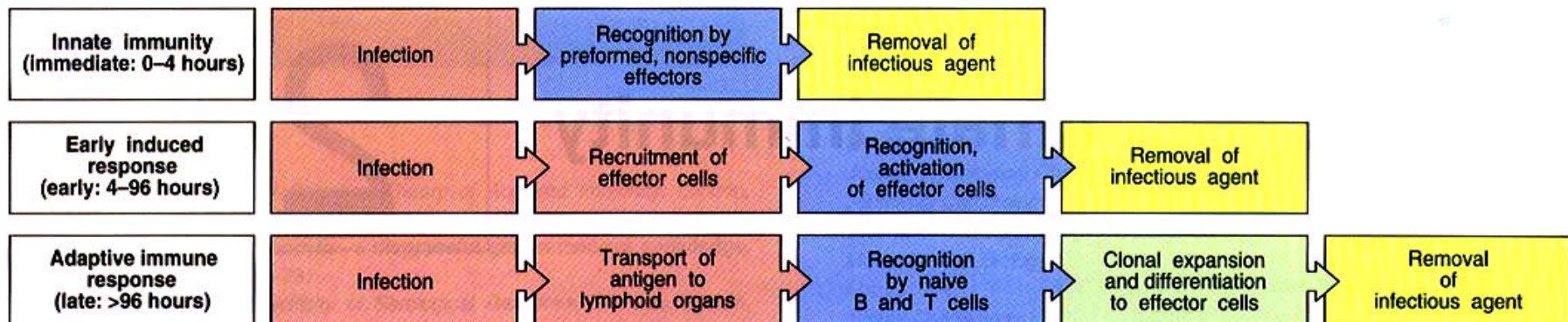
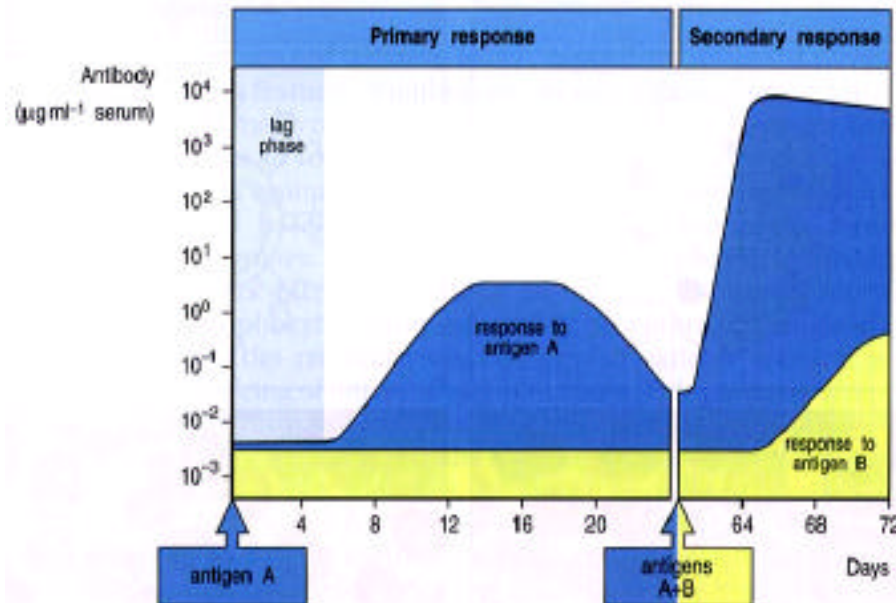


| Routes of infection for pathogens |   |   |   |
|-----------------------------------|---|---|---|
| Route of entry                    | Mode of transmission  | Pathogen  | Disease                                 |
| <b>Mucosal surfaces</b>           |   |   |   |
| Airway                            | Inhaled droplets  | Influenza virus<br><i>Neisseria meningitidis</i>  | Influenza<br>Meningococcal meningitis   |
| Gastrointestinal tract            | Contaminated water or food  | <i>Salmonella typhi</i><br>Rotavirus  | Typhoid fever<br>Diarrhea               |
| Reproductive tract                | Physical contact  | <i>Treponema pallidum</i>   | Syphilis                                |
| <b>External epithelia</b>         |   |   |   |
| External surface                  | Physical contact  | <i>Tinea pedis</i>  | Athlete's foot                          |
| Wounds and abrasions              | Minor skin abrasions<br>Puncture wounds<br>Handling infected animals                              | <i>Bacillus anthracis</i><br><i>Clostridium tetani</i><br><i>Pasteurella tularensis</i> | Anthrax<br>Tetanus<br>Tularemia         |
| Insect bites                      | Mosquito bites ( <i>Aedes aegypti</i> )<br>Deer tick bites<br>Mosquito bites ( <i>Anopheles</i> ) | Flavivirus<br><i>Borrelia burgdorferi</i><br><i>Plasmodium</i> spp                      | Yellow fever<br>Lyme disease<br>Malaria |



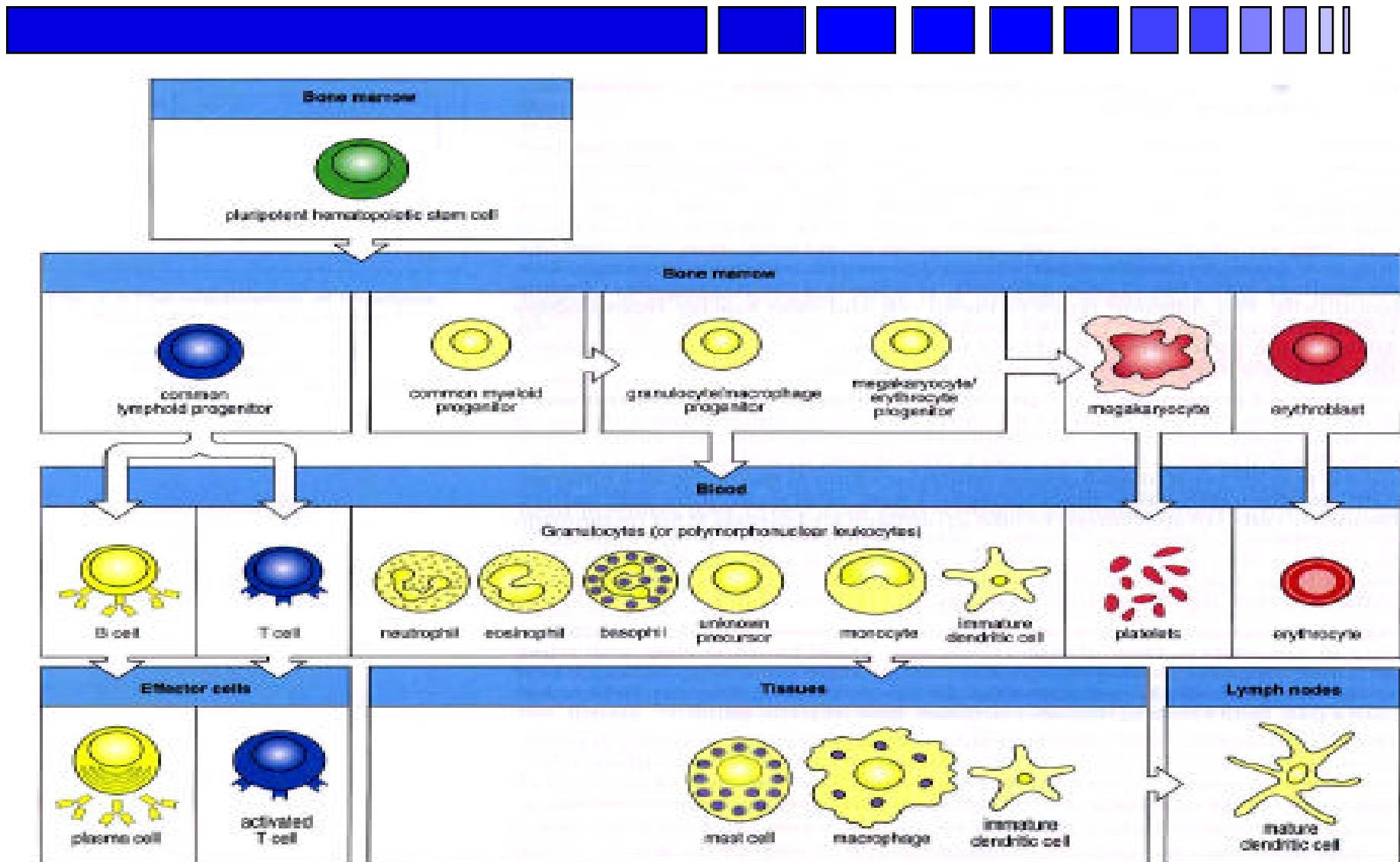
# Response of the Immune System

(from *Immunobiology*, Janeway et al, 2001)



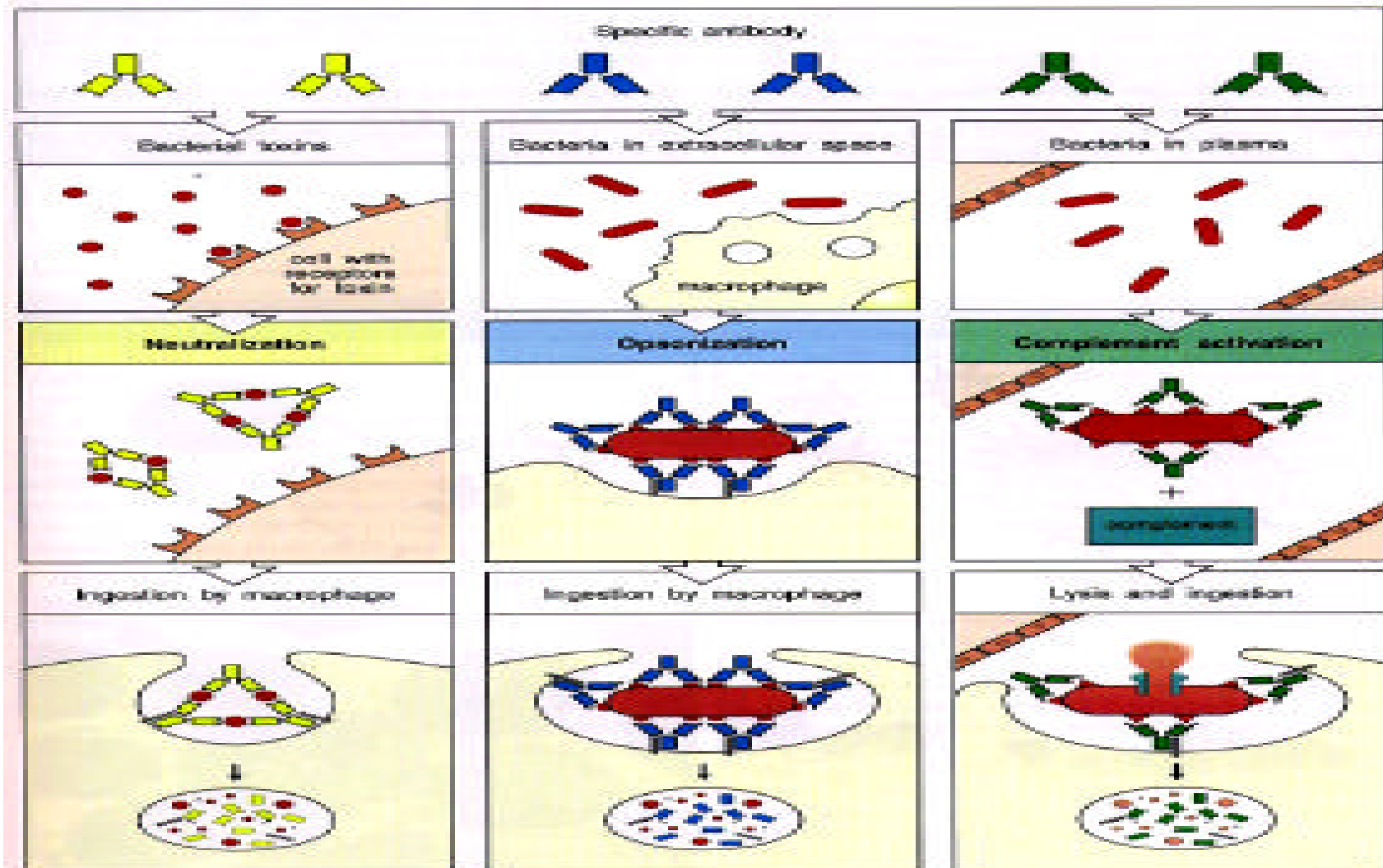
# Cells of the Immune System

(from *Immunobiology*, Janeway et al, 2001)



# Effects of Antibodies

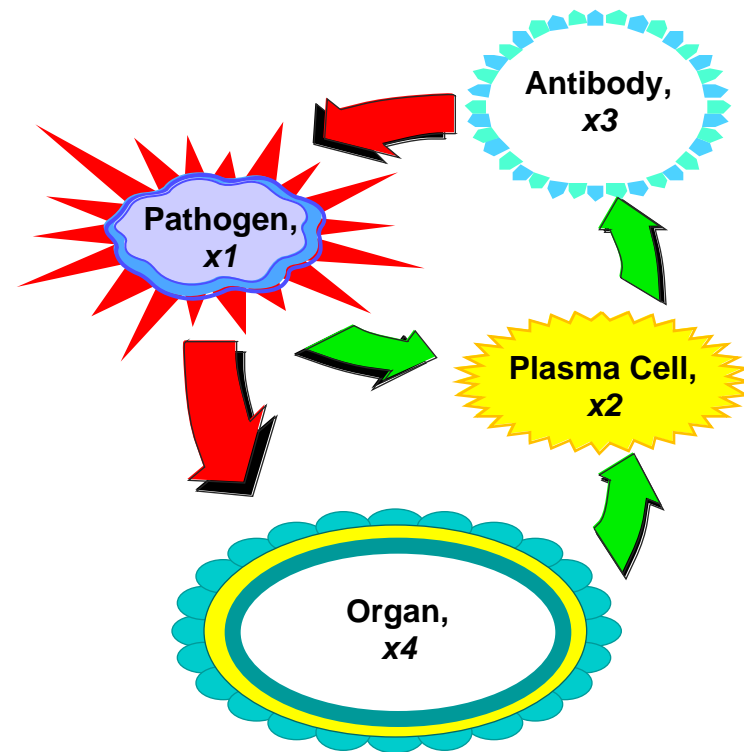
(from *Immunobiology*, Janeway et al, 2001)



# Dynamic Model for Generic Innate/Humoral Response to Pathogenic Attack

(w/ R. Ghigliazza, N. Kulkarni, O. Laplace)

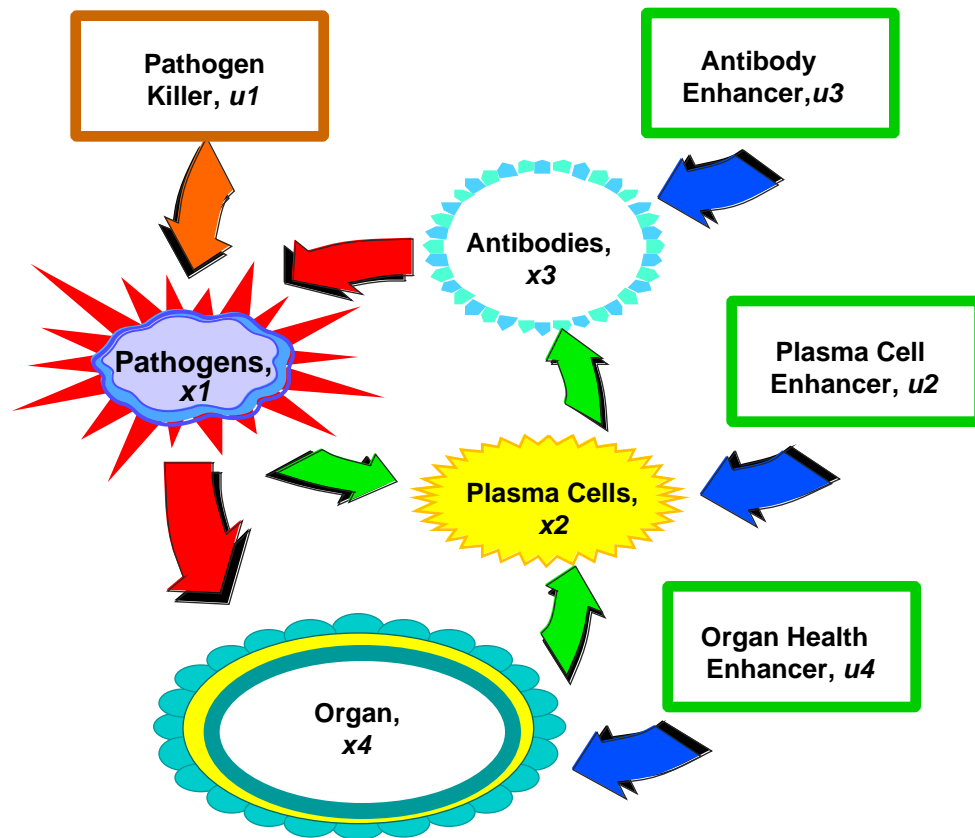
- $x_1$  = Concentration of a pathogen
- $x_2$  = Concentration of plasma cells, which are carriers and producers of antibodies
- $x_3$  = Concentration of antibodies, which kill the pathogen
- $x_4$  = Relative characteristic of a damaged organ  
[0 = healthy, 1 = dead]
- $x_i \geq 0$

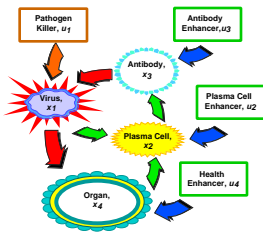


# Control Agents for Enhancing Innate Immune Response



- $u_1$  = Pathogen killer
- $u_2$  = Plasma cell enhancer
- $u_3$  = Antibody enhancer
- $u_4$  = Organ health enhancer
- $u_i \geq 0$





# Mathematical Model of Innate Immune Response w/Control Effects

(after Asachenkov *et al*, 1994)



$$\dot{\mathbf{x}}(t) = \mathbf{f}[\mathbf{x}(t), \mathbf{u}(t)]$$

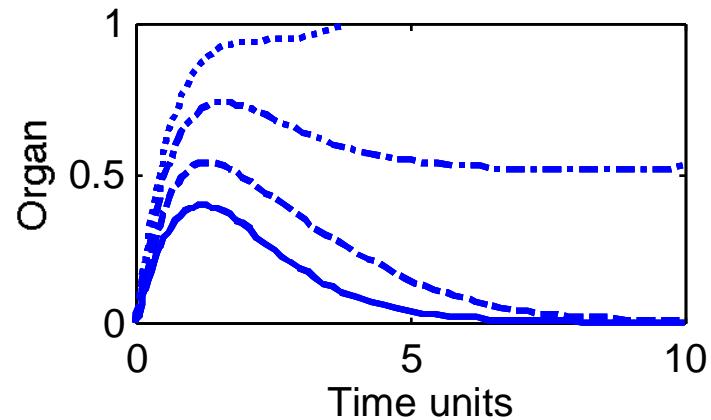
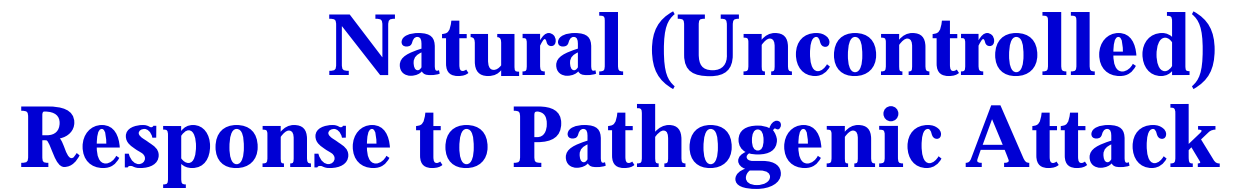
$$\dot{x}_1 = (a_{11} - a_{12}x_3)x_1 + b_1u_1$$

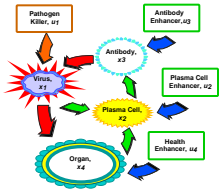
$$\dot{x}_2 = a_{21}(x_4)a_{22}x_1(t - \tau)x_3(t - \tau) - a_{23}(x_2 - x_2^*) + b_2u_2$$

$$\dot{x}_3 = a_{31}x_2 - (a_{32} + a_{33}x_1)x_3 + b_3u_3$$

$$\dot{x}_4 = a_{41}x_1 - a_{42}x_4 + b_4u_4$$

$$a_{21}(x_4) = \begin{cases} 1, & x_4 = 0 \\ \cos(\pi x_4), & 0 < x_4 < 1/2 \\ 0, & x_4 = 1/2 \end{cases} \quad \tau = 0$$





# Treatment Cost Function and the Optimal Control Policy



$$J = \phi[\mathbf{x}(t_f)] + \int_{t_0}^{t_f} L[\mathbf{x}(t), \mathbf{u}(t)] dt$$

$$J = \frac{1}{2} \left( p_{11} x_{1_f}^2 + p_{44} x_{4_f}^2 \right) + \frac{1}{2} \int_{t_0}^{t_f} \left( q_{11} x_1^2 + q_{44} x_4^2 + r_{11} u_1^2 + r_{22} u_2^2 + r_{33} u_3^2 + r_{44} u_4^2 \right) dt$$

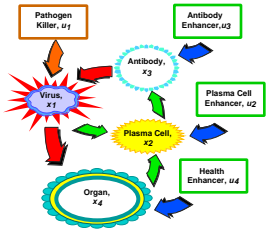
$$H(\mathbf{x}, \mathbf{u}, \lambda, t) = L(\mathbf{x}, \mathbf{u}, t) + \lambda^T \mathbf{f}$$

$$\dot{\lambda}(t) = - \frac{\partial H[\mathbf{x}(t), \mathbf{u}(t), \lambda(t), t]}{\partial \mathbf{x}}^T$$

$$\lambda(t_f) = \frac{\partial \phi[x(t_f)]}{\partial \mathbf{x}}^T$$

$$u_k = u_{k-1} - \epsilon \frac{\partial H}{\partial u}$$

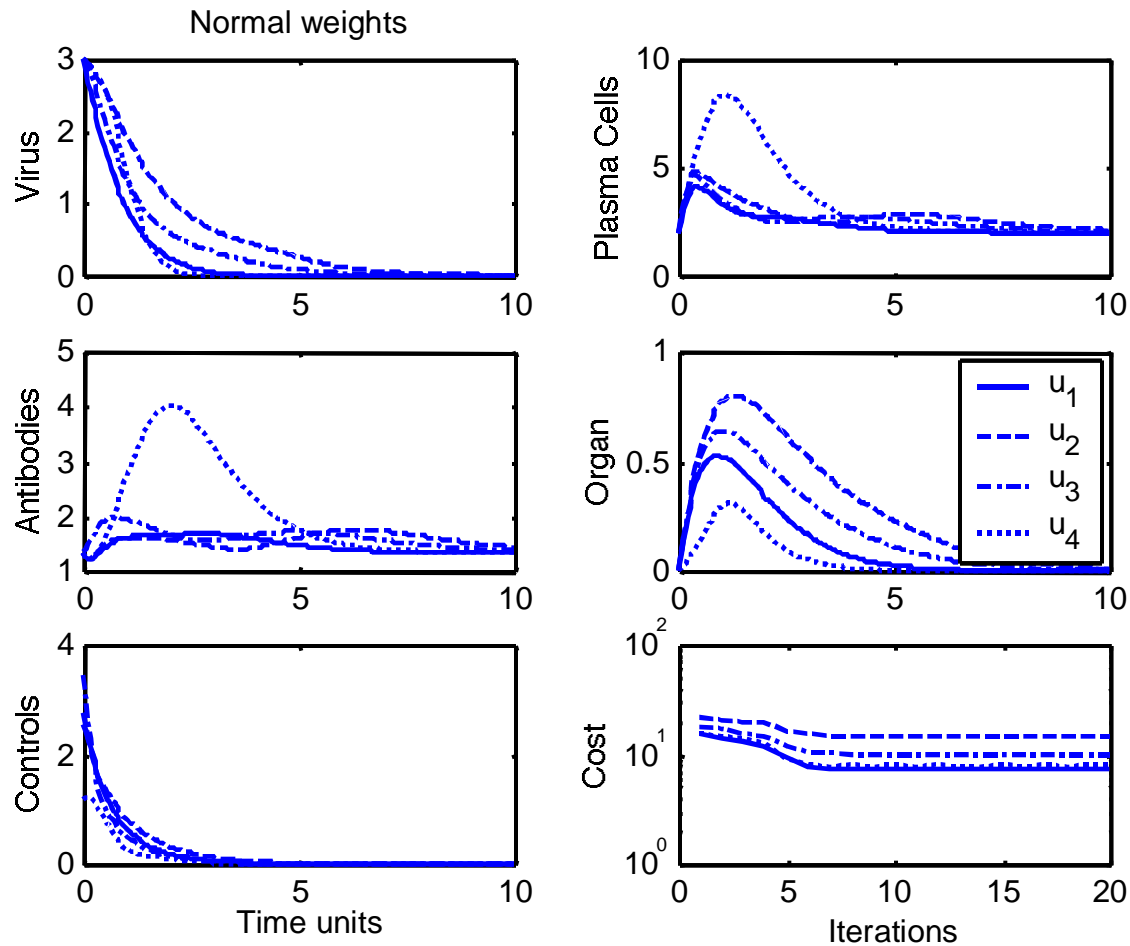
$$0 = \frac{\partial H[\mathbf{x}(t), \mathbf{u}(t), \lambda(t), t]}{\partial \mathbf{u}}$$



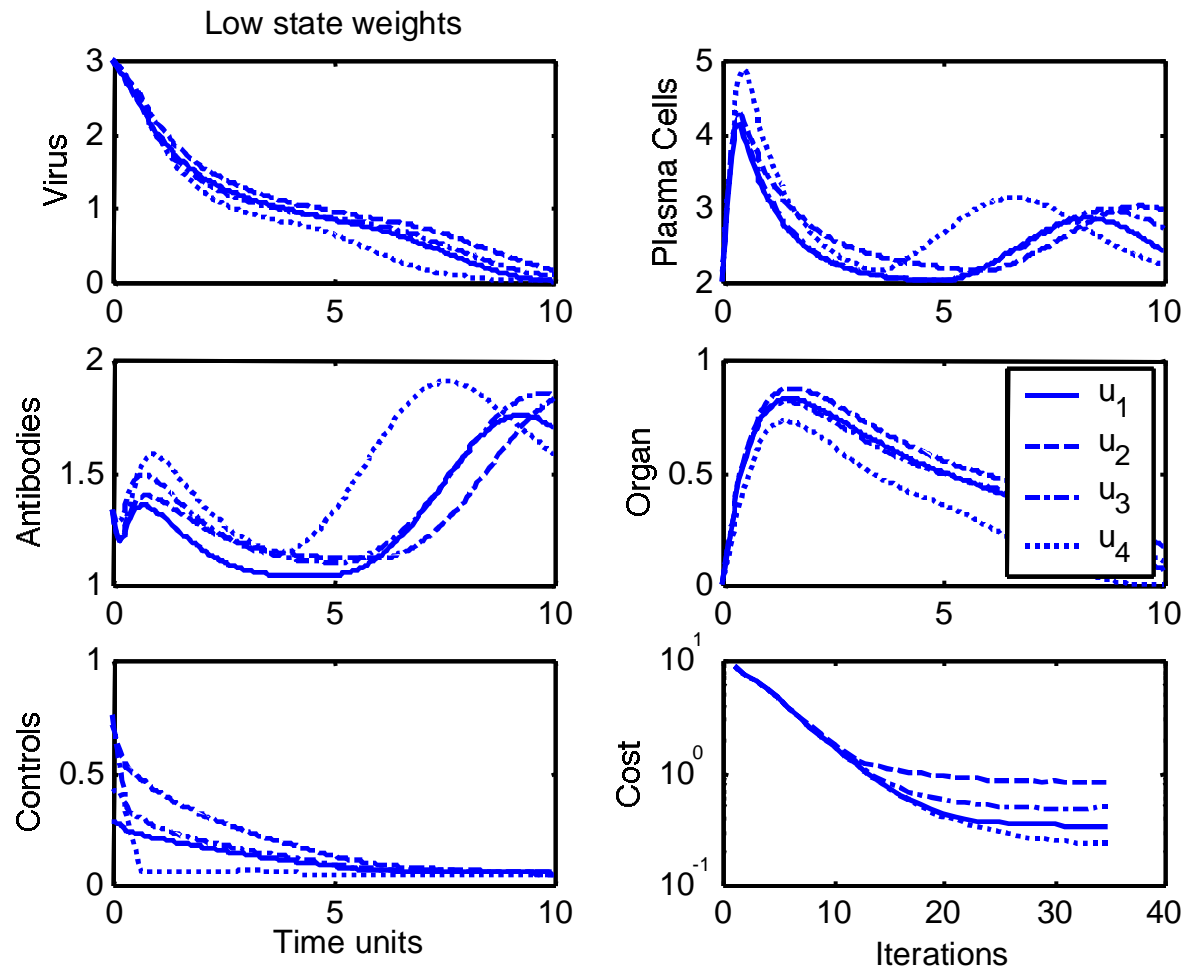
# The Cost Function and Its Optimization

- Steepest-descent, numerical generation of a deterministic optimal control history
- Tradeoff between dynamic response and application of control
- Quadratic cost penalizes large values more than small values
- Positive state and control constraints

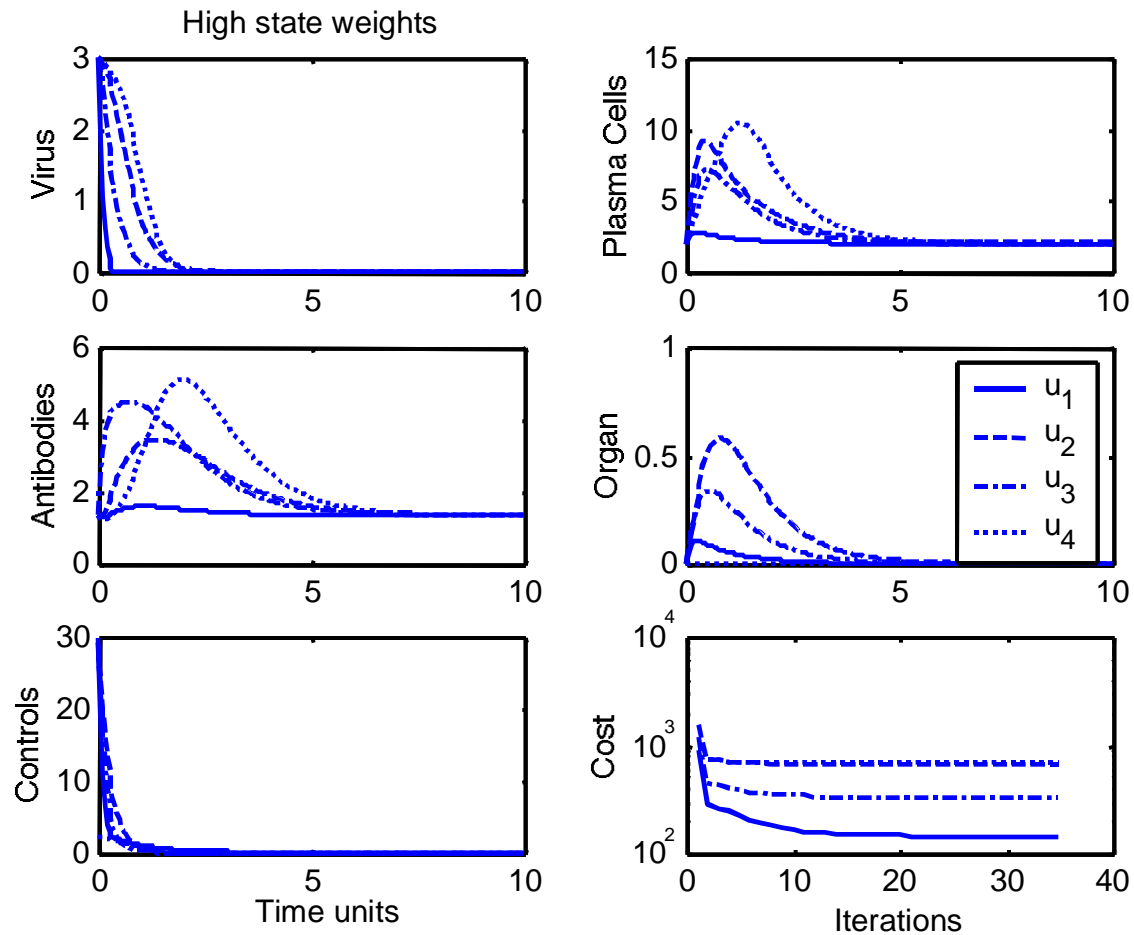
# Optimal Therapies with Unit Cost-Function Weights and Scalar Controls



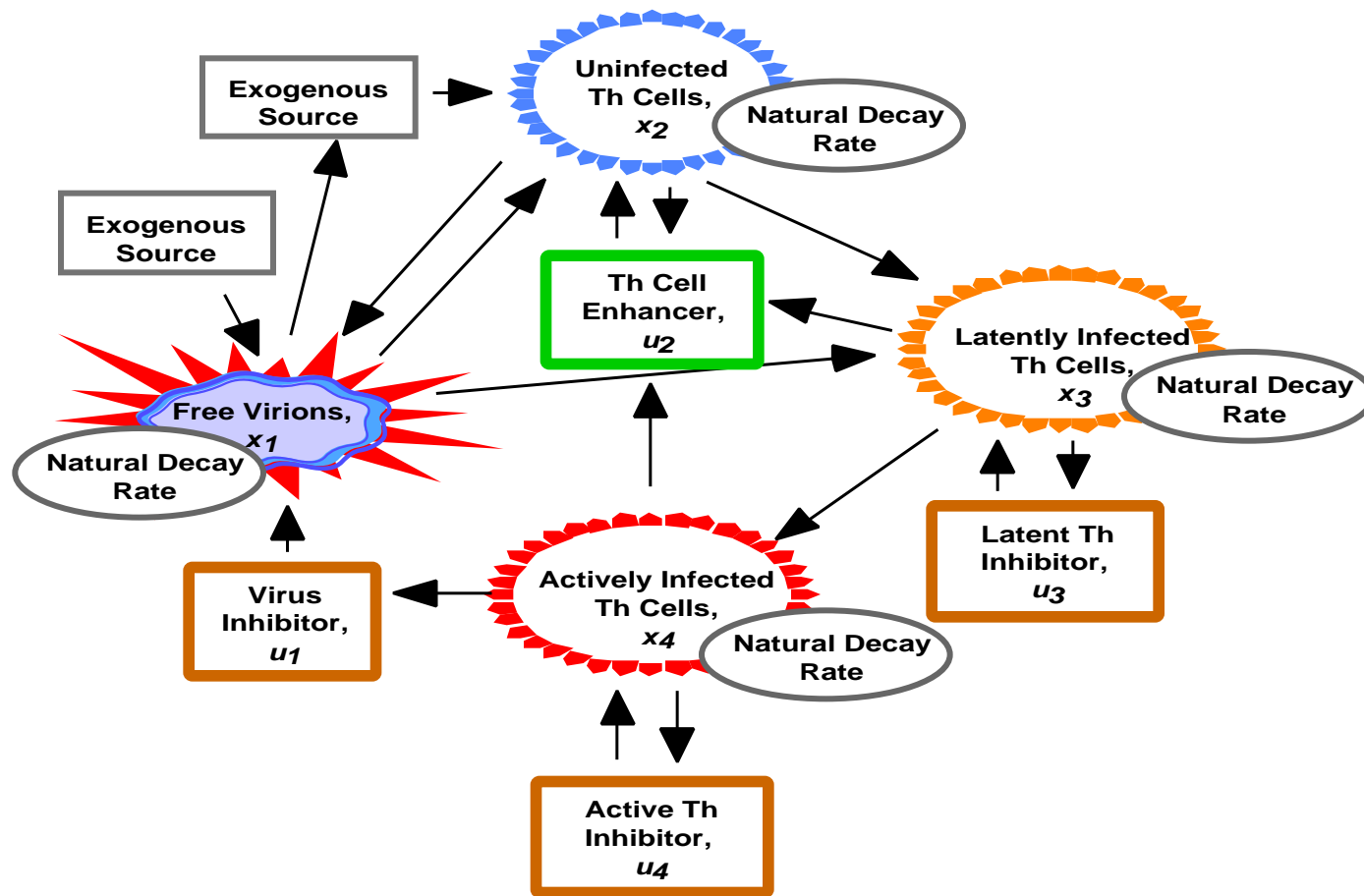
# Optimal Therapies with Integrand State Weights = 0.01 and Scalar Control



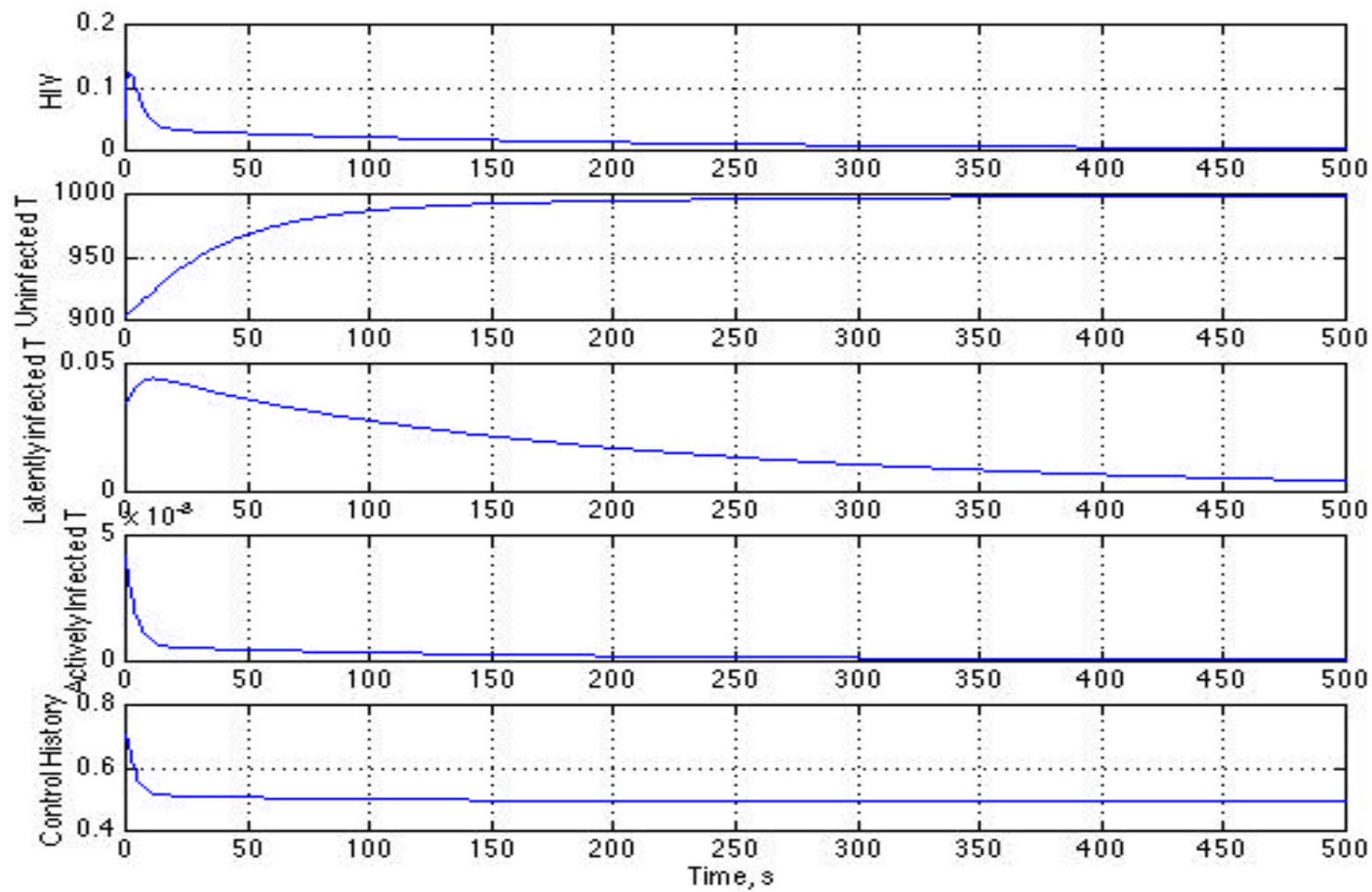
# Optimal Therapies with Integrand State Weights = 100 and Scalar Control



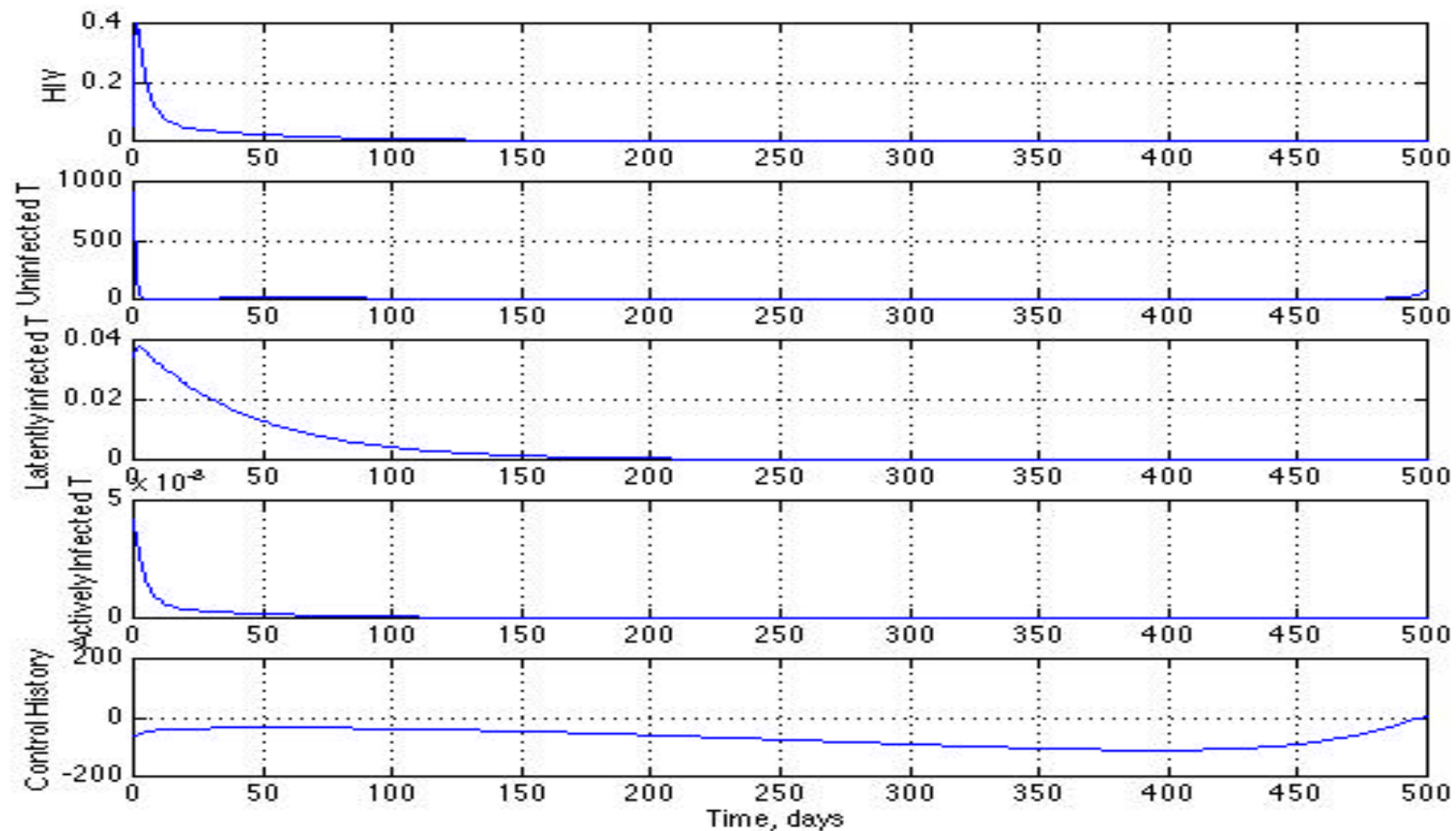
# Effect of Human Immunodeficiency Virus (HIV) on Helper T Cells



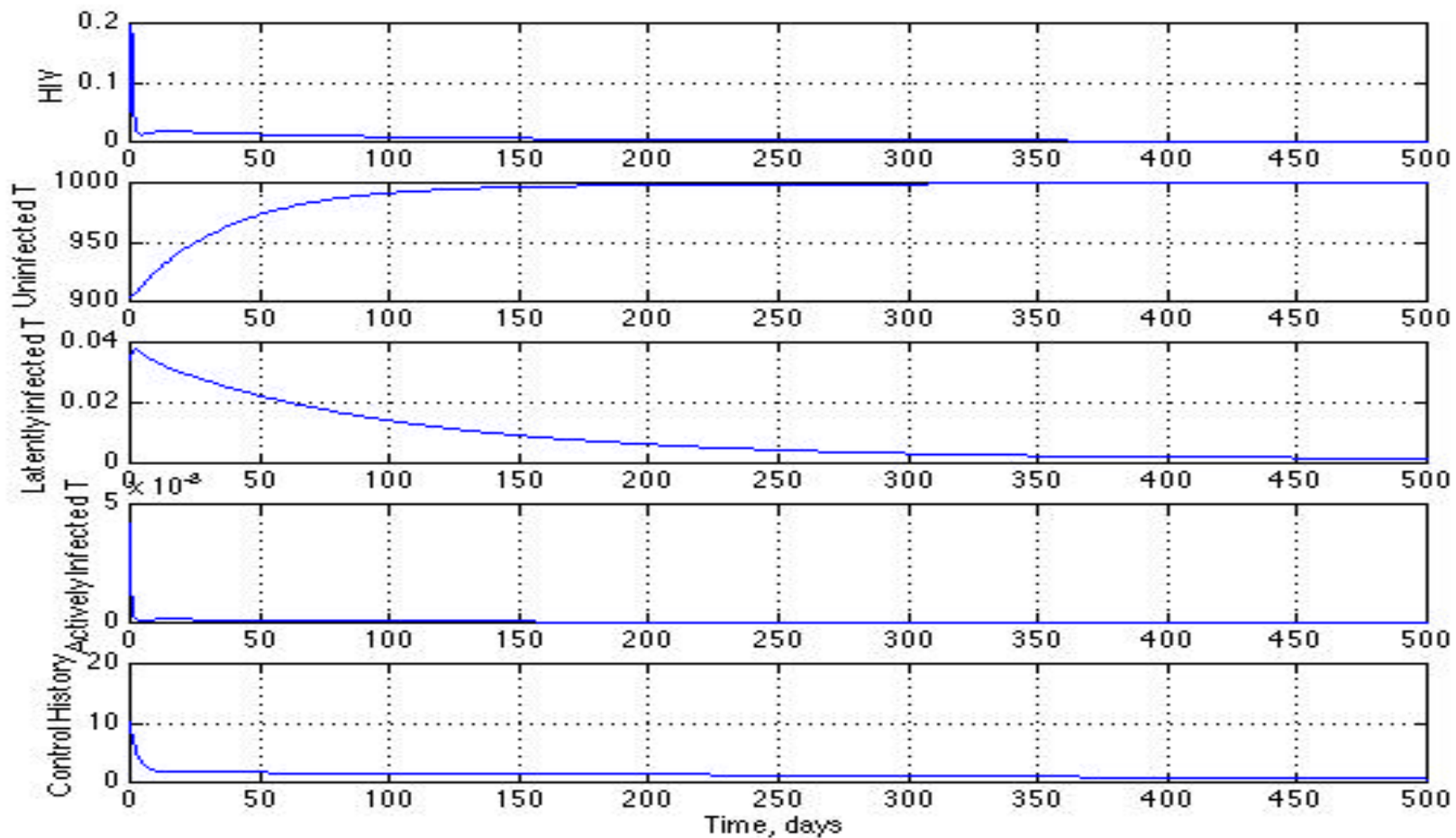
# Effect of Protease Inhibitor on HIV and Th Cell Populations

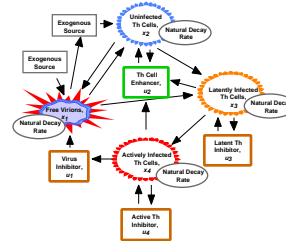
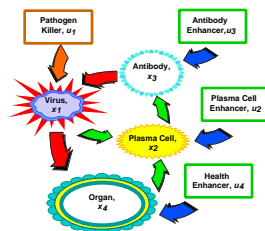


# Effect of Uninfected Th Control on HIV and Th Cell Populations



# Effect of Actively Infected Th Control on HIV and Th Cell Populations





## Conclusions

- Insights regarding the treatment of disease from mathematical models
- Criticality of reliable, accurate models
- Optimal control policies
  - Defeat or contain pathogenic assault
  - Augment natural function of the immune system
  - Attack the disease while minimizing harmful side effects
  - Allow physiological/monetary cost tradeoff between results of therapy and level of treatment
- Combined multi-drug therapy
- Patient-tailored therapy